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EFFECTS OF ETIOLOGICALLY DEFINED RESPIRATORY INFECTIONS ON LUNG FUNCTION AND ITS GROWTH IN AN AREA OF LOW AIR POLLUTION— SPIROMETRY IN YOUNG CHILDREN WHEN ILLNESS-FREE

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16. ABSTRACT

This longitudinal study was performed in a group of 3-12 year old children to document normal lung growth patterns as measured by spirometry. By clinical and laboratory parameters, these children were free of illness at the time of study and had been for the preceeding 21 days. Spirometry was performed prospectively over a period of six years in 69 children (27 black females, 23 black males, 10 white females, and 9 white males) all from a day care center. Eight hundred fifteen spirometric tests were made on these children. Six spirometric parameters were measured: forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), peak expiratory flow (PEF), forced expiratory flow during the middle half of the FVC ($FEF_{25-75\%}$), and maximum expiratory flows after 50% and 75% of the FVC have been exhaled ($\dot{V}max_{50\%}$ and $\dot{V}max_{75\%}$, respectively). There were significant differences between the regression lines (considering slope and intercept) for all six parameters when black females were compared to black males, white females to white males, black females to white females and black males to white males, except for $\dot{V}max_{75\%}$ for the comparison of black females to black males and white females to white males. These slopes and intercepts were similar to those reported by others for children of similar age and height. This study demonstrates that spirometry can be performed reliably at an early age in a day care center population, that there are significant racial and sexual differences in spirometric volume and flow parameters and that the variability of these measurements is proportional to height rather than being a constant.

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PREFACE

The long-term effects of air pollution on the respiratory health of children remain unknown. Many factors may be involved to explain this phenomenon. A major problem has been that not enough information has been collected describing the expected patterns of growth of measurable lung function parameters in a longitudinal fashion. In children, the recurrence of frequent respiratory illnesses may complicate these patterns. Additionally, the interactive effects of the ambient respirable atmosphere on the background of acute or chronic respiratory illness may alter growth patterns or may alter the expected variability of the measurements of lung function.

In 1966, The Frank Porter Graham Child Development Center was established to study the development in normal children as it relates to mental retardation. The facility was constructed on the campus of the Frank Porter Graham Elementary School and included a day-care program to which children were enrolled as young as six weeks of age. A medical program was also established to offer medical care to the children in the day care program. When the Center was opened, the Infectious Disease Division, Department of Pediatrics, University of North Carolina at Chapel Hill, began monitoring the respiratory illness patterns of the children enrolled in the day care program. These studies included monitoring clinical status on a daily basis, culturing upper respiratory tracts on a twice monthly basis and completion of a battery of serologic studies twice yearly. These studies were initiated to define the natural history of respiratory health in a population of normal children who could be closely monitored. To complement these studies and

to gain information about pulmonary function in children in a longitudinal study from an area relatively free of air pollution, Drs. John Knelson and John Brooks of the Clinical Studies Division of the Health Effects Research Laboratory set up a pulmonary function laboratory at the Center in 1971. Training to perform spirometry in the young children began at three years of age---two years earlier than is usually considered feasible in most populations. Lung volumes by helium equilibration were also started at five years of age. Although closing volumes were initially measured, this test was discontinued because of the high degree of intrasubject variability. In 1972, the Infectious Disease Division of the University of North Carolina Department of Pediatrics assumed this project under grant #R-802233 and this report documents the continuation of the collection of this data under grant #R-804577.

The data which have been analyzed for inclusion in this report have been collected over an eight-year period. Data have been collected continuously on all children who were initially enrolled in the study and additional children who have been enrolled in the study each year. The primary goal of this study has been to document several parameters of lung function in a longitudinal fashion in a group of normal children when they are illness-free. Because of the nature of respiratory illness in children, establishing the illness-free state is at times difficult but may be most closely approximated as afforded by the close monitoring of respiratory symptoms established in this population during this study. Secondary goals have been to establish the effects of growth on several

parameters of lung function. This information should provide useful reference material to the United States Environmental Protection Agency and also to other investigators.

ABSTRACT

Spirometry was performed prospectively over a period of six years in a group of 69 children (27 black females, 23 black males, 10 white females, and 9 white males) in a day care center, starting as early as two and a half years of age. Eight hundred fifteen spirometric tests were made on these 69 children when they were illness free. An average of 3.1 tests were made on each subject during each year of enrollment, and the subjects were enrolled in the study for an average of 3.5 years. Linear regression analysis by a method of weighted least squares was found to adequately describe the data over a height range of 100-150 cm and was performed on six spirometric parameters: forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), peak expiratory flow (PEF), forced expiratory flow during the middle half of the FVC ($FEF_{25-75\%}$), and maximum expiratory flows after 50% and 75% of the FVC have been exhaled ($\dot{V}max_{50\%}$ and $\dot{V}max_{75\%}$, respectively). Ninety-five percent confidence limits for the regression lines and 95% prediction intervals for individual observations were also computed. There were significant differences between the regression lines (considering slope and intercept) for all six parameters when black females were compared to black males, white females to white males, black females to white females and black males to white males, except for $\dot{V}max_{75\%}$ for the comparison of black females to black males and white females to white males. These slopes and intercepts were similar to those reported by others for children of similar age and height. The 95% confidence limits and 95% prediction intervals were proportional to height and were similar to estimates of

parameter variability reported by others. This study demonstrates that spirometry can be performed reliably at an early age in a day care center population, that there are significant racial and sexual differences in spirometric volume and flow parameters and that the variability of these measurements is proportional to height rather than being a constant.

This final report was submitted in fullfillment of Grant #R-804577 by The University of North Carolina under the sponsorship of the United States Environmental Protection Agency. This report covers the period from August 1, 1976 to April 30, 1980 and was completed as of April 30, 1980.

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SECTION 1

INTRODUCTION

The growth of the lung in children is a dynamic process characterized by an increase in alveolar number followed by an increase in size of airways and air spaces in the lung. Bucher and Reid (1) and Reid (2) have shown that the total number of airways is the same in children and adults. The total complement of bronchial generations is present by the end of the sixteenth week of gestation and the spaces which will contain air begin to change to an alveolar pattern during the latter part of gestation. During the first weeks of life, typical alveoli appear and lung growth for the first four years of life consists predominantly of an increase in alveolar number. At this point, increase in lung size changes to a pattern of growth consisting of an increase in size of airways and alveoli. The physiologic importance of this growth pattern has been demonstrated by Hogg et al. (3) who found that the conductance of peripheral airways (behond the fifteenth bronchial generation) increases dramatically at about five years of age, while no change occurs in the central airways.

Most reference data for pulmonary function tests in children have been generated on new borns and on children over five or six years of age (4,5). Pulmonary function tests from infancy to five years of age have not been well documented and it is not known what effect the relative lower conductance of the peripheral airways might have on measurements of lung function. It is also not known what effects acute respiratory illnesses might have on measurements of pulmonary function

and if these effects are more easily detected because conductance of the peripheral airways is lower. Williams et al. (6) have shown that the peripheral fraction of total respiratory resistance measured by the forced random noise technique in a group of children, whose average age was 46 months, to be significantly greater than in a group of children whose average age was 61 months. (Conductance of the peripheral airways was less in the younger children than in the older children.) Collier et al. (7) have demonstrated a greater number of significantly decreased spirometric parameters during acute upper respiratory illness in a group of children less than 84 months of age, as compared to a group of children greater than 84 months of age. These data suggest that there are differences in lung function during early life attributable to developmental phenomena in the airways and that these differences may be important in the manifestation of disease.

Additionally, data of pulmonary function in children have been collected in a cross-sectional fashion. No data exists which has been systematically generated in a longitudinal fashion. These data are important to determine if lung function development in children progresses in a predictable fashion much the same as height and weight development, or if the growth of the lung might progress in another as yet undetermined pattern.

This report outlines the analysis of the spirometry data collected over a six-year period at the Frank Porter Graham Child Development Center. Only information gathered on the children when they were well has been included in this analysis. The data has been analyzed in a cross-sectional fashion so that later analyses can be performed to determine what the

relationships of each individual child's growth pattern is to the overall growth pattern. Because of the known effects of race and sex on lung function, the children have been separated into four groups for these analyses: black females and males and white females and males.

SECTION 2

CONCLUSIONS

The results of this study on lung growth as measured by spirometry in a longitudinal population of children in an area of low environmental pollution have demonstrated:

1. The feasibility of obtaining reproducible spirometric tests of lung function in small children as young as three years of age.
2. Significant racial and sexual differences in most spirometric parameters of lung function in young children.
3. That regression lines of spirometric parameters of lung function can be adequately described in young children by a linear regression over the height range of 100-150 cm.
4. That paramters of variability are proportional to height rather than being a constant over the region of interest.

SECTION 3

RECOMMENDATIONS

1. In studies examining the effects of acquired insults to the lung, more reference data for tests of pulmonary function from children who have been documented to be illness-free at the time of testing and for a finite period prior to testing need to be developed.
2. The effects of specific insults on the growth patterns of various parameters of lung function need to be documented in longitudinal studies.
3. Methods need to be developed for performing tests of pulmonary function in relatively uncooperative children younger than five years of age.
4. Statistical methods for describing longitudinal data collected at unevenly spaced intervals need to be developed.
5. Reference data for tests of pulmonary function need to be collected in a longitudinal fashion in illness-free, nonsmoking individuals 13-25 years of age, living in an area relatively free of atmospheric pollution.

SECTION 4

METHODS

Subjects for this study were selected prior to birth from volunteer parents who were permanent residents of Chapel Hill. Psychologists and educators who direct the Frank Porter Graham Child Development Center's child-development studies were responsible for recruitment of the children who participated in this project (8). Six to twelve children were admitted to the population each year as early after six weeks of age as possible. At the time of selection for the study, informed consent was obtained from the parents for participation in both the developmental studies and in the respiratory illness and physiology studies. The parents could decline participation in the respiratory illness and physiology components of the Center's program.

Complete clinical and microbiologic documentation of each child's respiratory illness experience was maintained from the time of enrollment in the Center. Trained observers monitored the children five days a week for signs of illness and the parents were encouraged to report any illnesses experienced on weekends and during vacations. Upper respiratory tract cultures were performed every two weeks for bacteria, viruses and mycoplasmas and additionally during acute respiratory illnesses.

Training of the subjects to perform spirometric maneuvers began at three years of age. When their performance revealed that they could reliably reproduce their "best" forced vital capacity within 5-10% on three to five successive days, they were included in the respiratory physiology study. If their performance after a period of training proved unpredictable, further training was delayed for a six-month period.

Spirometry was performed in the standing position using a nose-clip. The spirometer was a ten liter rolling seal spirometer (Med-Science Model 465) with a flow signal output. The flow signal was sampled 80 times per second and stored in a Digital Equipment Corporation PDP-12/40 computer. The digitized flow signal was integrated numerically to provide a volume signal. These data were analyzed using the algorithm of Domizi and Earle (9) and Earle and associates (10) to obtain forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), peak expiratory flow (PEF), forced expiratory flow during the middle half of the FVC ($FEF_{25-75\%}$), maximum expiratory flow after 50% of the FVC had been exhaled ($\dot{V}max_{50\%}$) and maximum expiratory flow after 75% of the FVC had been exhaled ($\dot{V}max_{75\%}$). All values for respiratory parameters were corrected to BTPS conditions. The flow-time curve, the flow-volume curve and the computed pulmonary function parameters were displayed immediately for evaluation of technical quality. The flow signal and the computed parameters from the effort with the largest FVC which was technically adequate were stored on computer tape in the PDP-12/40 computer. An electronic calibration was performed before each test. The system was calibrated with a one liter syringe on a weekly basis.

Seventy-three subjects were studied at three-month intervals. Additional studies were performed with any acute respiratory illness and at one month following the illness. The data collected during respiratory illnesses and during the 21 days following a respiratory illness were excluded from this analysis. The duration in the study ranged from one to six year. Fourteen hundred one spirograms were included in the data file and 815

spirograms were used for this analysis. Spirograms were not included in this analysis for the following reasons: technical quality (113 tests), tests performed during illness (361 tests), tests on three known asthmatic subjects (69 tests), tests on one excessively obese subject (36 tests), and tests performed on children older than 13 years or on children greater than 160 cm tall (7 tests).

For data analysis, an initial study was performed to select appropriate regression models using the pulmonary function parameters FVC, FEV_1, PEF, $FEF_{25-75\%}$, $\dot{V}max_{50\%}$, and $\dot{V}max_{75\%}$ as dependent variables and a variety of functions of height and of weight as independent variables. Separate models were fit for the four race/sex combinations: black females (BF), black males (BM), white females (WF) and white males (WM). The criterion for selecting an appropriate model was the average estimated variance (AEV) (11) using the observed height and weight data to define the region of interest and its weight function. In all cases, for the range of height from 100-150 cm, straight line regressions with height as the only independent variable were selected as best fitting the data. Polynomials in height and weight, logarithmic models, and various combinations did not improve the regression statistics.

Each pulmonary function parameter exhibited a pattern in which the standard deviation was approximately proportional to height. Consequently, analyses were based on weighted regressions using 1/height to weight each observation. The data from the four race/sex groups were incorporated into one general linear multivariate model (GLMM) with the six pulmonary function parameters as dependent variables. The model included one intercept and one slope (i.e., one straight line) for each race/sex group by pulmonary function parameter combination. Weighting of each observation was performed by standard GLMM methods using the LINMOD package (12). This technique

produces a pooled estimate of the variance-covariance matrix (over race/sex groups).

Standard statistical methods for constructing regression confidence bands do not reflect the proportionality of the standard deviation to the independent variable. A new statistical method was developed to determine confidence regions with width proportional to height over the height range of 100-150 cm (13). This procedure was used to produce 95% confidence bands for regression lines and 95% prediction bands for future observations.

SECTION 5

RESULTS

The data used in this analysis were collected during a longitudinal study in a day care center. Only data collected when the children were well have been included in this analysis. Over the six-year study period, 69 children were followed for an average of 3.5 years each and had spirometric measurements performed 815 times. These 69 children included 27 black females (BF), 23 black males (BM), 10 white females (WF), and 9 white males (WM). The children in general were 90 to 155 cm tall and spanned an age range of 2 1/2 to 12 years. The average height for each year of age of the total population in the study is shown in Table 1, as well as the numbers of observations made on the total population during each year of age. The number of spirometric measurements performed during each year of age for the four individual race/sex group measurements and the number of children on which these measurements were made are also shown in Table 1. This table demonstrates the overall age distribution of the children during the six years of observation. The average number of measurements for each year of age for the total group was 3.14 and ranged from 3.07-3.25 for the 4 race/sex groups demonstrating a similarity of frequency of study for the 4 race/sex groups.

The regression coefficients and standard errors of the six spirometric parameters computed by weighted least square analysis for the four race/sex groups are shown in Table 2. The coefficients for the 95% confidence

limits and 95% prediction limits are also listed. Plots of each discrete data point along with the regression lines and 95% confidence and prediction intervals for each parameter in each of the four race/sex groups are demonstrated in Figure 1. Although some of the data in each group are outside the height limits of 100-150 cm, the regressions lines have been computed to only describe the region for each of the four race/sex groups from 100-150 cm in height. Comparisons of the plots of the regressions for the four race/sex groups are shown for each parameter in Figure 2. In general, the regression lines for the white children lie above the regressions for the black children for each parameter. The p-values for the tests of no difference comparing the regression lines (including slope and intercept) between the important race/sex groupings for each spirometric parameter are shown in Table 3. All of these comparisons are significantly different except for $\dot{V}max_{75\%}$ for black females compared to black males and white females compared to white males. The p-values for the tests of no difference comparing the slopes of the regression lines are shown in Table 4 for these same important groups. These comparisons reveal a different pattern. The slopes for all four comparisons for $\dot{V}max_{75\%}$ are not significantly different. Comparisons of the slopes of the regressions for FVC for WF vs. WM and BM vs. WM, for FEV_1 for BM vs. WM, and for PEF for BF vs. WF do not reveal significant differences.

To compare the values for the regression coefficients obtained by weighted analysis to classically used methods for computing linear regressions, regression coefficients were computed using unweighted linear least squares analysis. These values, as shown in Table 5, are similar to the values shown in Table 2. The correlation coefficients (r^2) and the standard deviations are also shown. The mean values of each parameter for

each group were also computed so that the relative variability for each parameter would be computed as the coefficient of variation (C.V.). These values are also shown in Table 5.

SECTION 6

DISCUSSION

This study was conducted on a group of normal children over a six-year period and included multiple observations on each subject. Although the children have been studied in a longitudinal fashion, the data included in this report have been analyzed using techniques which are usually used in analyzing cross-sectional data. Analysis was conducted using these techniques to provide a basis on which to compare individual growth profiles and the effects of intercurrent respiratory insults.

The statistical analyses used in this study have incorporated some methods not traditionally used in the analysis of pulmonary function data. Previously, a wide variety of regression functions have been used to describe the various parameters of pulmonary function as a functions of height, weight and other measures of physical size. Most of these studies have been reviewed by Polgar and Promadhat (4) in 1971 and more recently by Polgar and Weng (5). In most cases, analysts have used some form of stepwise regression together with the R^2 statistic to compare possible models (regression functions). The R^2 statistic does not include information about the intended use of the regression line, the region of interest (range of values of independent variables over which one wishes to draw inferences), or other factors

important to the selection of variables in a regression model. There is a wide agreement (14) that other model-comparison criteria such as the Average Estimated Variance (A.E.V.) (11), Mallows' Cp (15), and others are more appropriate in many circumstances.

In this analysis, the region of interest was set a priori at 100-150 cm height range and 12-40 kg weight range. Not all areas in this region are equally important; other aspects being equal, the investigators felt the regression lines should generally have a better fit where the preponderance of the data occured and not be required to fit so well in regions with less data. As a consequence, the A.E.V. statistic (11) was chosen as a criterion for comparing various models; the second order moment matrix $M = (X'X)/N$ was used to represent the region-of-interest and weight function required to use the A.E.V.

A variety of polynomial and logarithmic-exponential models were initially fit to the data. For each functional form of these models, including forms with linear and quadratic terms in both height and weight, 24 models were fit: 2 race groups x 2 sex groups x 6 pulmonary function parameters. The A.E.V. statistic was computed for each model, along with R^2, t-tests for individual terms in the model, and p-values for these terms. In many cases, it was possible to detect slight departures from straight-line relationships. For example, for the black female group, the quadratic term in height was significantly different from zero for PEF. (The data, with fit polynomials of degree 1 through 4, are shown in Figure 3.) However, the principal intended use for the regression lines is not to determine whether the mean PEF (or other parameter) is or is not a straight line function of height over the range 100-150 cm but to use the regression line as a "prediction function" with corresponding confidence

limits and prediction intervals, which can be used to estimate mean PEF (or other parameter) for given height values within the region of interest.

A regression used as a prediction function has two sources of error: (1) the variance in a predicted mean value (uncertainty in the exact location of the "true" line), which arises from the random variability in the original data and which is reflected by the width of the confidence bounds about the regression line; (2) the bias of a predicted value, which arises from using a relatively simple function, such as a straight line, in place of the true (unknown) response function, which is almost certainly curvilinear and more complicated. (The R^2 statistic does not reflect either of these sources of error.) In regression problems, a model with fewer terms will typically have a smaller prediction variance and a larger prediction bias than a model with more terms. However, it is frequently the case that the deletion of some statistically significant terms from a model produces a simpler model with drastically reduced prediction variance and only sightly increased prediction bias.

The case of PEF for black females provides an example in the present case. The regression coefficients for orthogonal polynomial (in which each term is already "adjusted for" all the others) through degree four are shown in Table 6 along with standard errors, t-test values, and two-tail p-values. Note that the constant, linear and quadratic coefficients are significantly different from zero at the 0.05 level. The A.E.V. value for a regression represents a weighted average of the variance of a predicted value plus the squared bias of a predicted value (i.e., an average of the total squared error of prediction), averaged over the region of interest. A regression with a smaller A.E.V. is "better" for

prediction purposes than one with a larger A.E.V. The A.E.V. values for the four regressions, linear through quartic as functions of height, are shown in Table 7. Note that even though some of the higher order terms are statistically significant, which means we detect nonlinearity, the straight line is best for the present purposes. In Figure 3, one can see that the curvature of the quadratic through quartic regression lines is slight compared to the variability in the data.

Although a wide variety of regressionfunctions were compared, including logarithmic, exponential, polynomials in various combinations of height, weight, and age, for the present purposes over the region of 100-150 cm height range, a straight line regression was best in every case. If a wider region of interest were used, with data throughout the region, one would expect the curvilinear nature of the response functions to be sufficiently marked to require a curvilinear regression for a good fit.

Examination of the data plots in Figure 1 clearly shows that variability of the pulmonary function parameters increases with height. Ignoring this aspect of the data, a violation of the usual assumptions for regression analysis, would result in estimators with poorer precision (greater variances) than estimators from properly weighted regression. The relationship between variance and height was examined by obtaining the absolute values of the residuals from an unweighted regression fit; an absolute residual is an approximate estimate of the standard deviation of the pulmonary function parameter at that height. The absolute residuals were regressed on height to determine how variance varies as a function of height. The results varied with the pulmonary function parameter, but in general the standard deviation was found to be very nearly proportional to

height. As a result, all analyses were performed using weighted general linear model (least squares) analysis and 1/height as the weighting variable.

Several types of between-group comparisons can be made from the general linear model approach. For notation, consider the example where:

a_{ij} denotes the intercept of the regression line for the i-th race group (i=1 for black, i=2 for white) and j-th sex group (j=1 for females, j=2 for males) and

b_{ij} denotes the slope of the regression line for the i-th race and j-th sex group.

If the FVC results for black subjects (i=1) are considered, the following null hypotheses might be tested:

(1) Ho_1: $a_{11} = a_{12}$, i.e., no difference in the FVC intercepts for black females and males;

(2) Ho_2: $b_{11} = b_{12}$, i.e., no difference in the FVC slopes (growth rates) of black females and males.

(3) Ho_3: $a_{11} = a_{12}$ and $b_{11} = b_{12}$, i.e., the FVC regression line for black females and males; and

(4) Ho_4: $\hat{y}_{11}(122) = a_{11} + 122b_{11}$
$= \hat{y}_{12}(122) = a_{12} + 122b_{12}$,
i.e., estimated FVC at height = 122 cm is the same for black females as for black males.

Hypothesis Ho_3 is of interest because it addresses the question: is the mean response of FVC to height identical for the two groups over the height range 100-150 cm, or is it different in any way (intercept and/or slope)?

The null hypothesis will be declared false if there is sufficient evidence that either Ho_1 is false or Ho_2 is false. Even if there is not quite sufficient evidence to reject either Ho_1 or Ho_2, the combined evidence on both issues may be sufficient to reject Ho_3.

Ho_4 is of special interest. Since each race-sex group has its own regression line (separate intercepts and slopes) for each pulmonary function parameter, another way of looking at the differences between groups is to select a particular height and make comparisons at that height. Due to different slopes, comparisons at one height might lead to different conclusions than for comparisons made at another height.

Two groups might be considered significantly different in one sense if Ho_3 were rejected; one would conclude the groups exhibit a different response (e.g., mean FVC) to changes in height, or different "growth curves". In contrast, if Ho_4 is rejected, one would conclude the two groups have different mean FVC's when compared at the mean height of the group.

One of the assumptions of the general linear model analysis is that every FVC observation is correlated with every other FVC observation, and similarly for the other pulmonary function parameters. If subjects are assumed to be a random sample from some larger population, then any two FVC measurements from the same subject are correlated, a violation of the linear model assumptions. When measurements are made at regularly spaced intervals, a multivariate model may properly be used for analysis (16, 17) and in some circumstances a univariate repeated measures analysis is appropriate (18, 19, 20). The asymptotic methods of Kleinbaum (21) are applicable to situations in which observations are made at irregular intervals, as in this case. For finite-sample data no statistical method

provides an exact analysis for data such as these; the analyst must choose one of several approximate methods. Both experience and theoretical work (20, 22, 23, 24) have shown that even for moderate within-subject correlation, up to $\rho \simeq 0.30$, the critical value of the F-test statistic is not greatly affected if one uses a univariate model approach, i.e., one assumes a zero within-subject correlation. Estimates of within-subject correlations in these data vary, especially with the time interval between pulmonary function tests, but a randomized block approach to estimating intra-class correlation shows correlations to be well below the 0.30 level. Thus, the use of univariate methods is justified as a suitable, sufficiently accurate approximation for the analysis of these data.

The children in this population were closely monitored and had their respiratory illnesses rigorously documented. Because respiratory illnesses occur more frequently during the winter months, the frequency of obtaining measurements on these children when illness-free might be less during the winter months than during the summer months. Figure 4 demonstrates the number of measurements made during each month of the year. The number of measurements made during the winter months are at least equal to the number of measurements made during the summer months for the group as a whole and for each race/sex group. The decreased number during July and August probably reflects the vacation period for laboratory personnel and subjects alike and does not represent an increased frequency of illness.

Over half of the children in the study have been followed more than three years, as shown in Figure 5. Seventeen children have been followed

for the duration of the study. In general, the black children have been in the study a shorter period of time than the white children. This shift in the racial character of the population represents the results of selection criteria which resulted in the recruitment of more black children than white children during recent years of the study.

The regressions have been computed for the rather limited height range of 100-150 cm. In general, this height range is over a shorter span of height than is reported by most other investigators, which reflects the younger age range included in this analysis. We found that a linear regression model fit our data as well as curvilinear models, but we did not have a significant amount of data in children taller than 150 cm, which is at the point where lung growth appears to begin to accelerate. If the height region below 150 cm for other investigators (4, 5, 25, 26, 27) is studied, a straight line appears to fairly closely approximate the lines described by their regressions. For heights above 150 cm, a greater slope is needed to describe the regressions. Also, for heights below 100 cm, lower slopes will be necessary to adequately describe the vital capacities of younger children because the regressions coefficients given in Table 2 for FVC yield negative values at 50 cm height, the approximate length of a new born infant.

The regression lines for FVC's for the white children in this study lies within two standard deviations of the regressions Polgar and Promadhat (4) developed from means of other investigators. The regressions for the black children are significantly different (Table 3) from the white children, and they fall outside the two standard deviation ranges in Polgar and Promadhat's data. Hsu et al. (26), Binder et al. (28), and Schoenberg et al. (29) also have documented that FVC and FEV_1 values for black children

are less than for white children. In our studies, we found that the differences between the races and between the sexes were not so predictable for flow values (PEF, $FEF_{25-75\%}$, $\dot{V}max_{50\%}$ and $\dot{V}max_{75\%}$) and Hsu (26), Binder (28), and Schoenberg (29) have come to a similar conclusion in the data they present.

We have been concerned about characterization of the variability about the regression lines. Polgar and Promadhat (4) have found the standard deviation of the average of regressions values obtained by several other investigators to be about 7% of the mean value. They also averaged the intersubject standard deviations for FVC reported by several investigators and this was thirteen percent. Their regression lines obtained by averaging the data reported by other investigators with the associated variability bands are best utilized for comparison of the average values obtained in a laboratory and probably should not be utilized for prediction of the normal state. In this case, one standard deviation interval would be expected to be about thirteen percent of the value for FVC at the mean FVC for the population being studied in the laboratory. However, a problem develops when the extremes of the population are considered. At the mean of the population, the absolute value of the standard deviation is about thirteen percent of the mean value; but at the shorter heights, the absolute value of the standard deviation becomes a larger percentage of any expected values for FVC, and at taller heights, the absolute value of the standard deviation becomes a smaller percentage of any expected FVC. We have calculated the coefficient of variation (SD ÷ Mean x 100) for all parameters for the four race/sex groups computed by the unweighted least squares analysis and have listed them in Table 5.

Our values of the coefficient of variation for FVC for the four race/sex groups range from 14-17%, which are slightly larger than the value reported by Polgar and Promadhat (4). To compare the values for the coefficients of variation in Table 5 obtained by classical statistical methods with the prediction intervals computed in Table 2, we have computed the percent of the expected value for FVC from the four race/sex groups represented by the 95% prediction interval given in Table 2. The values expected for FVC at both extremes and in the middle of the height range of interest, the value for the 95% prediction intervals and the percent of the expected FVC represented by the 95% prediction intervals are given in Table 8 for the four race/sex groups. At a height of 125 cm (the mid-range of the region of interest), the 95% prediction interval represents about two times the value obtained for one coefficient of variation shown in Table 5. This is as expected, since the value of one coefficient of variation represents one standard deviation and the 95% prediction interval represents two standard deviations. Even though the 95% prediction intervals shown in Table 2 and 8 are proportional to height, they still represent a larger percentage of the FVC for heights below the mid-range and a smaller percentage of the FVC for height above the mid-range as shown in Table 8.

Most investigators have not reported data regarding flows at low lung volumes (e.g. $\dot{V}max_{50\%}$ and $\dot{V}max_{75\%}$). Recently, Schoenberg et al. (29) have published rather complicated regressions for spirometric parameters, including flows at low lung volumes for black and white children. Hsu et al. (26) have also published regression coefficients for PEF and $FEF_{25-75\%}$ for black and white children, but they did not publish results of flows after 50% and 75% of the FVC had been exhaled. Zapletal et al. (27) have

published flow data for white males and females only. Michaelson et al. (30) have reported data for $\dot{V}max_{50\%}$ and $\dot{V}max_{75\%}$, but their data represents only combined data for white male and female children. The data for PEF, $FEF_{25-75\%}$, $\dot{V}max_{50\%}$ and $\dot{V}max_{75\%}$ for the 4 race/sex groups in our study (present study) as compared to Schoenberg et al. (29), Zapletal et al. (27), and Hsu et al. (26) at height values of 130 and 150 cm are shown in Table 9. The data for the present study were computed from the regression coefficients in Table 2. There is a close correspondence between our values and Schoenberg's and Zapletal's values for $\dot{V}max_{50\%}$ and $\dot{V}max_{75\%}$ for white children and between ours and Schoenberg's for black children. Our values lie intermediate between Hsu's and Schoenberg's for PEF. There is a close association between our values and Hsu's values for $FEF_{25-75\%}$ for the 4 race/sex groups. Regression coefficients for $FEF_{25-75\%}$ were not reported by either Schoenberg or Zapletal. The reasons for the discrepancy between our data and Hsu's, Zapletal's and Schoenberg's data for PEF are not clear. Differences in measuring and recording devices and population characteristics may explain part of these discrepancies.

In summary, we have described the results of spirometric data collected in a longitudinal fashion from a mixed racial population in a day care center. These data have been collected on a younger population than has been previously described. Over ranges of height comparable to other reports, these data are similar to those obtained by other investigators. The variability of these data is also similar and is not reduced because of the longitudinal nature of the study.

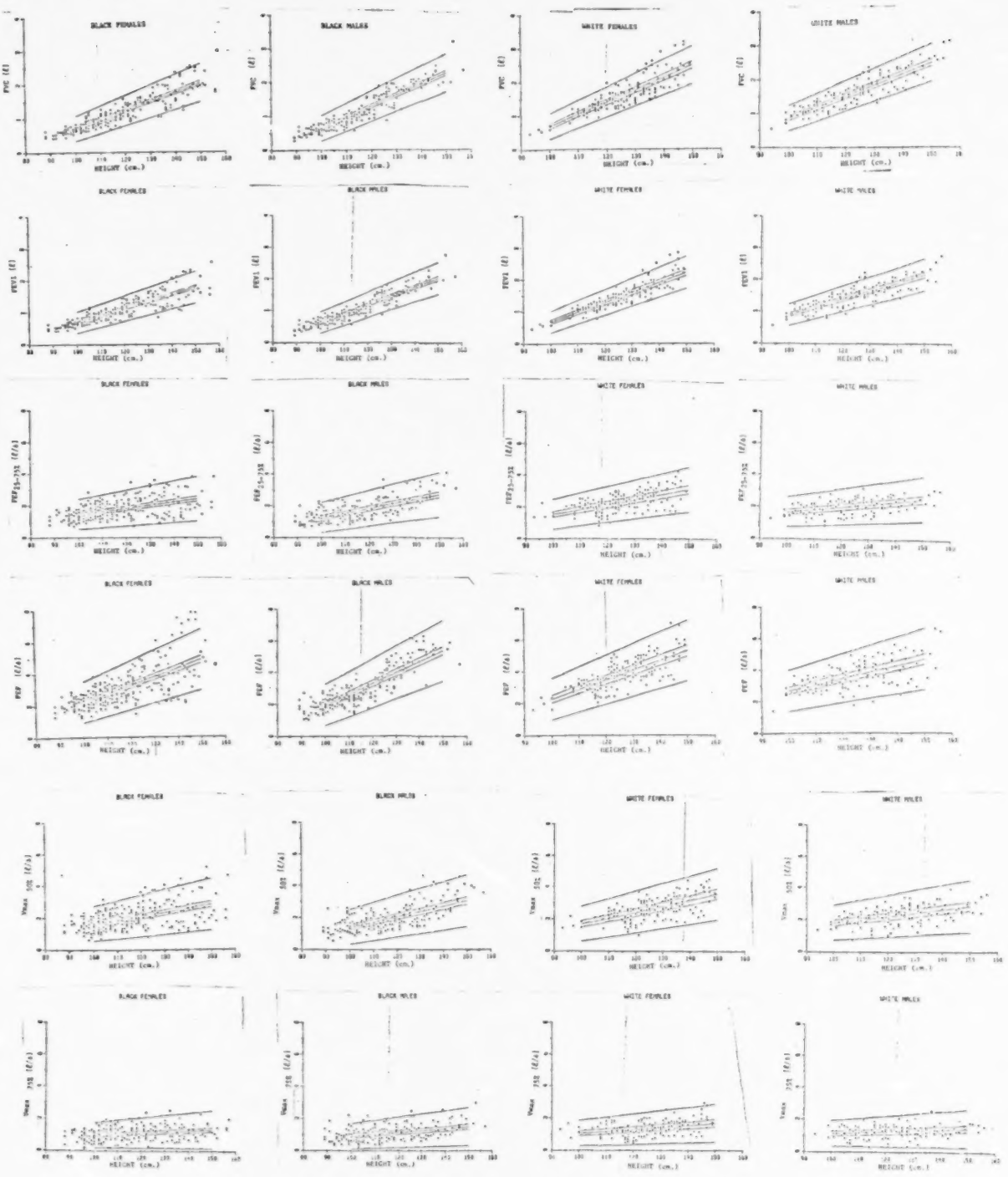


Figure 1. Scatter plots of the raw data for each of the 6 spirometric parameters from the 4 race/sex groups. The central lines are the linear regression lines, the 2 intermediate lines are the 95% confidence limits for the regression lines and the 2 outside lines are the 95% prediction limits for an individual observation.

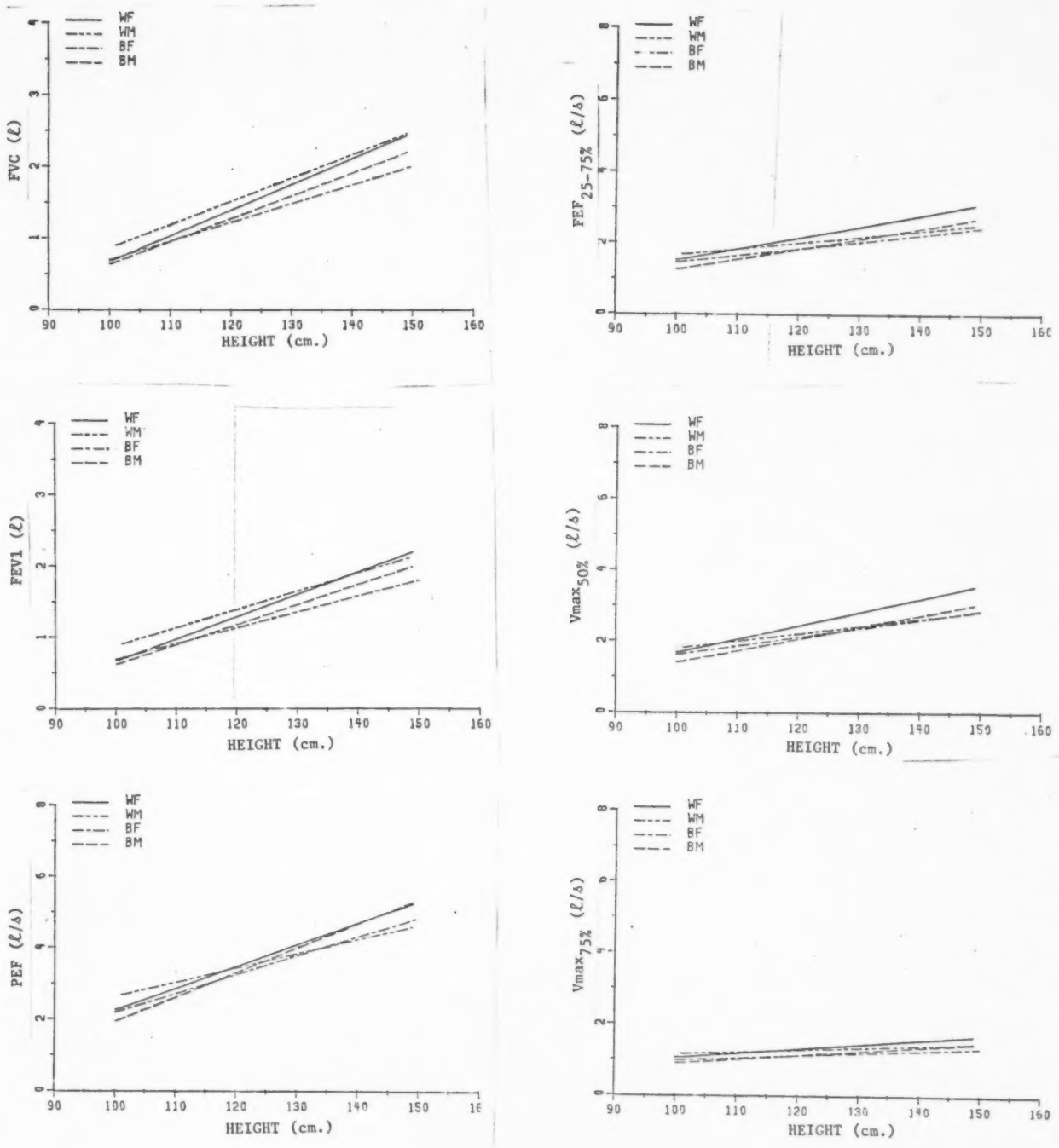


Figure 2. Comparisons of the regression lines from the 4 race/sex groups for each of the spirometric parameters.

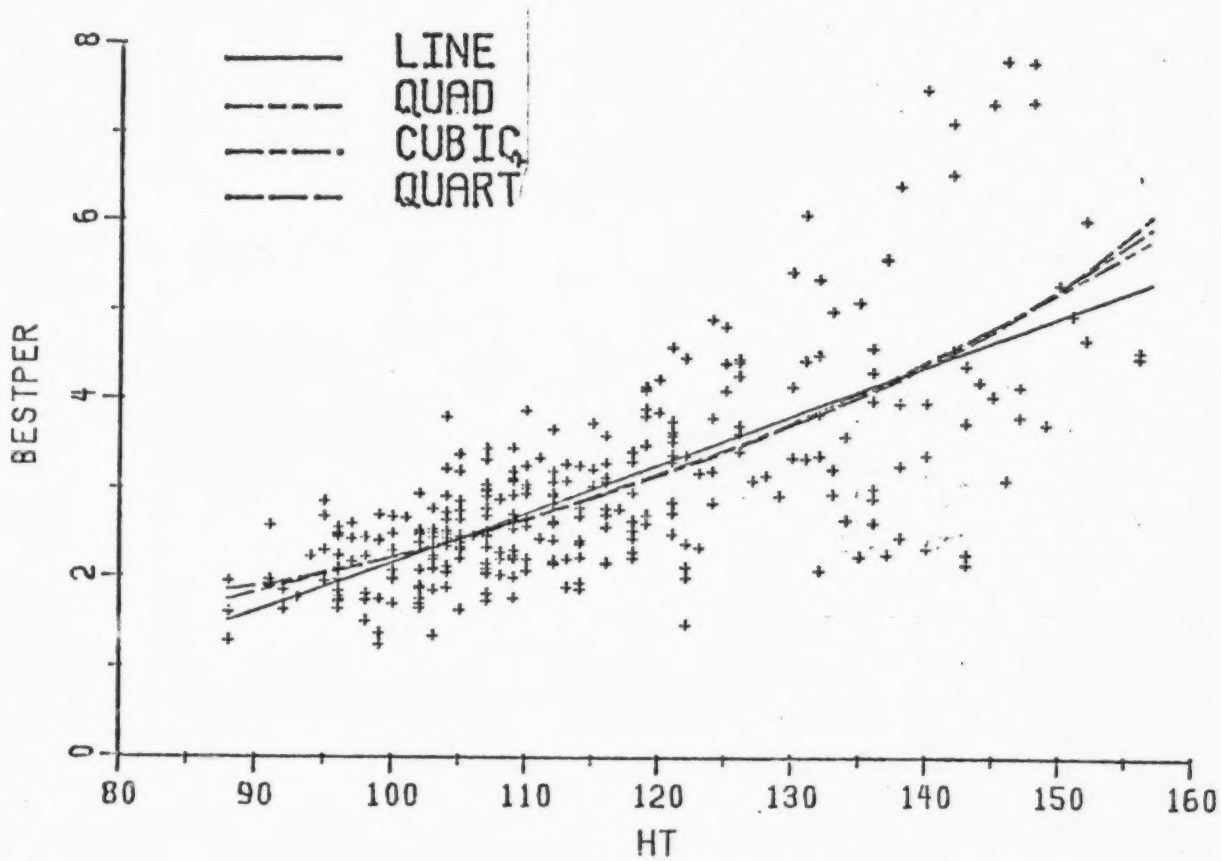


Figure 3. Plot of the data points for peak expiratory flow from black females and demonstration of the "fit" of the linear, quadratic, cubic and quartic regression lines using height as the independent variable.

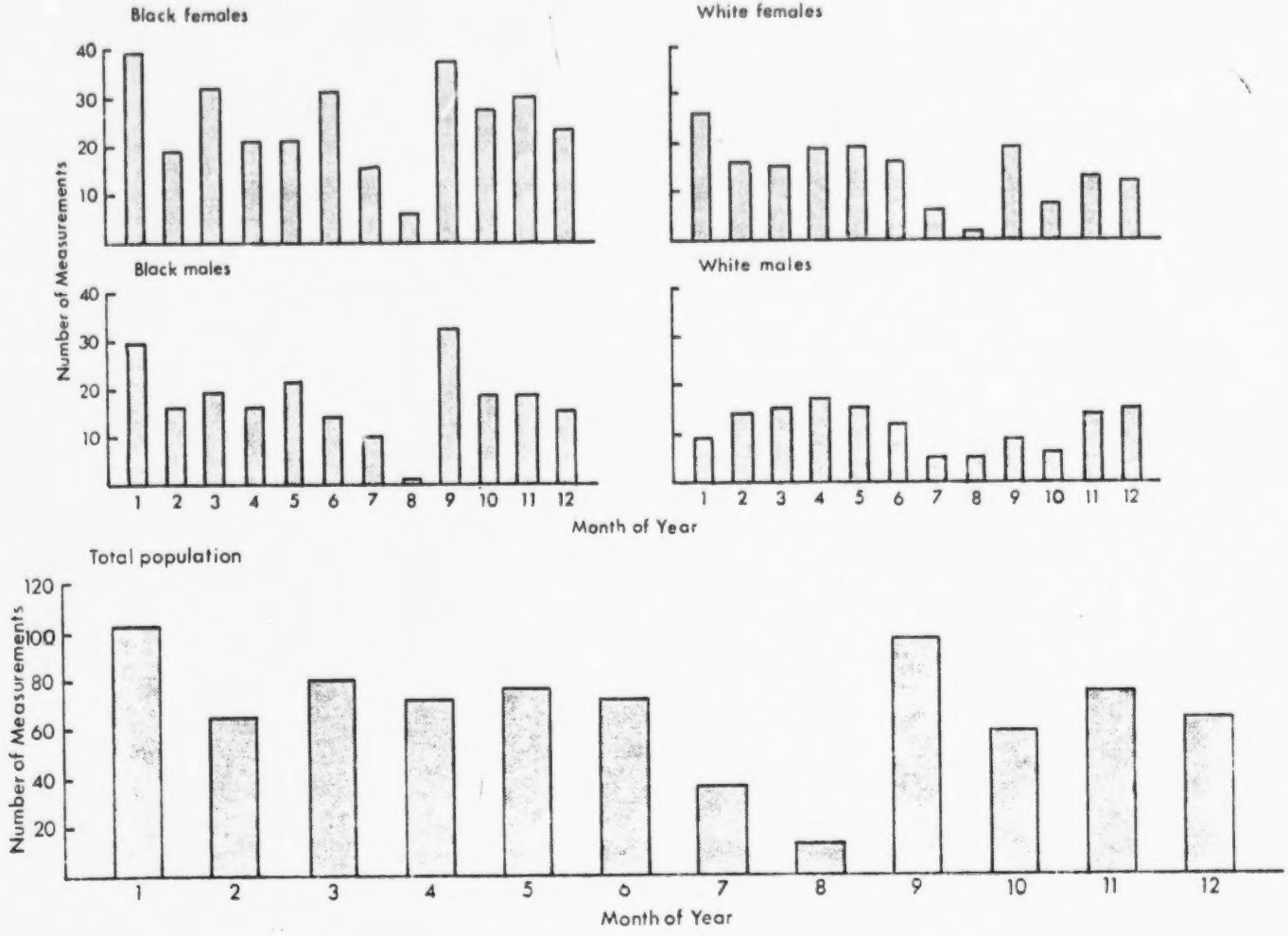
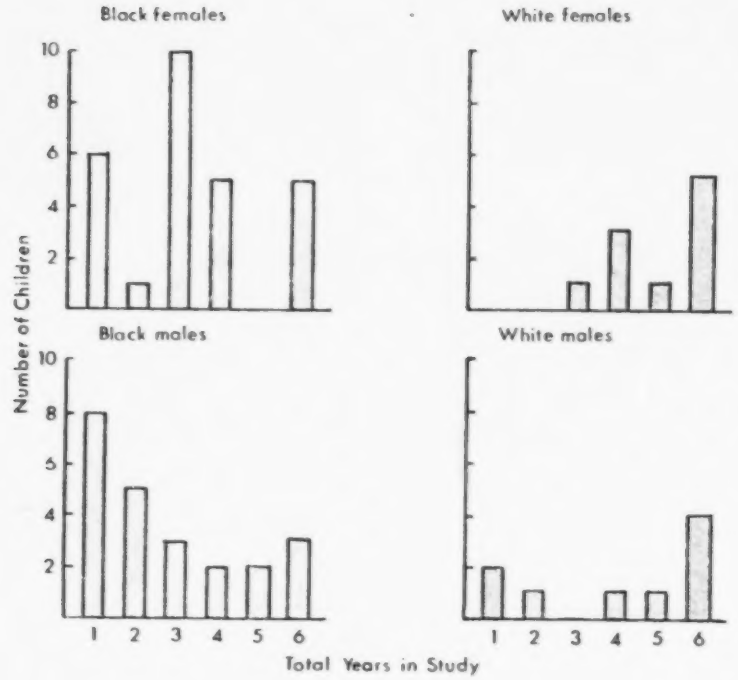


Figure 4. Number of spirometric tests performed each month of the year for the total population and for each of the 4 race/sex groups.



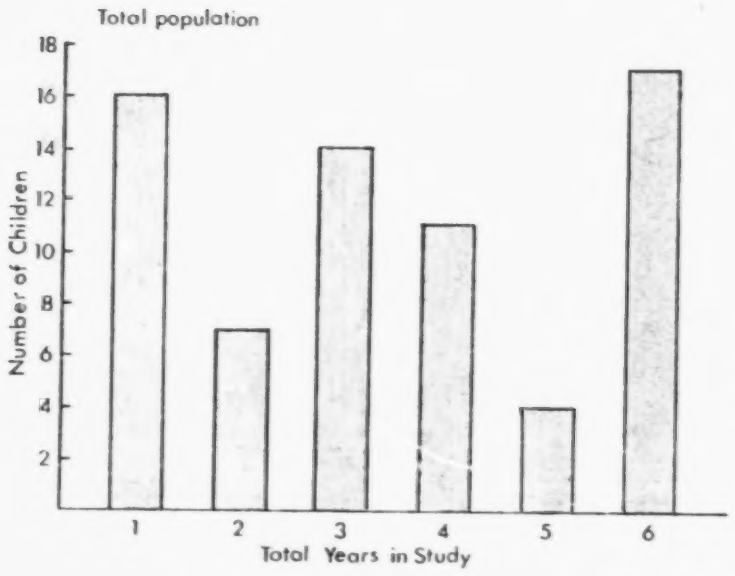


Figure 5. Number of children and length of time in the study for children in the total population and also for the children in each of the 4 race/sex groups. No child is represented more than 1 time in either of the components of these duration distributions.

TABLE 1

AVERAGE HEIGHT, NUMBER OF CHILDREN STUDIED AND
NUMBER OF OBSERVATIONS PER YEAR OF AGE DURING THIS STUDY

	Total Population			Black Females		Black Males		White Females		White Males	
Age	Avg. Ht.	#Child.	#Obs.	#Child.	#Obs.	#Child.	#Obs.	#Child.	#Obs.	#Child.	#Obs.
<3	92	7	16	3	9	3	6			1	1
3	99	30	102	16	60	11	33	1	5	2	4
4	107	45	152	22	75	14	48	4	12	5	17
5	114	42	139	20	58	11	37	5	17	6	27
6	119	31	104	12	33	7	26	7	25	5	20
7	125	24	83	6	17	5	17	7	28	6	21
8	130	26	74	8	21	4	10	8	26	6	17
9	135	21	56	6	15	4	10	6	19	5	12
10	141	17	50	3	10	3	11	7	19	4	10
11	145	14	33	2	3	4	10	6	17	2	3
12	151	2	4					1	1	1	3

TABLE 2

WEIGHTED REGRESSION COEFFICIENTS* FOR SPIROMETRIC PARAMETERS

	BLACK FEMALES				BLACK MALES			
Parameter††	b***	m†††	K† ($\times 10^3$)	L** ($\times 10^2$)	b	m	K ($\times 10^3$)	L ($\times 10^2$)
FVC, ℓ	-1.966±0.084	0.0267±0.0008	0.415	0.371	-2.601±0.100	0.0324±0.0009	0.485	0.372
FEV_1, ℓ	-1.533±0.076	0.0222±0.0007	0.378	0.334	-2.191±0.090	0.0281±0.0008	0.437	0.335
PEF, ℓ/sec	-3.112±0.290	0.0531±0.0026	1.477	1.281	-4.913±0.343	0.0685±0.0031	1.692	1.284
$FEF_{25-75\%}$, ℓ/sec	-0.493±0.211	0.0195±0.0019	1.041	0.931	-1.650±0.246	0.0292±0.0022	1.231	0.933
$\dot{V}max_{50\%}$, ℓ/sec	-0.820±0.245	0.0245±0.0022	1.213	1.084	-1.888±0.291	0.0330±0.0026	1.478	1.087
$\dot{V}max_{75\%}$, ℓ/sec	0.243±0.177	0.0073±0.0016	0.865	0.781	-0.297±0.209	0.0119±0.0019	1.032	0.783

	WHITE FEMALES				WHITE MALES			
Parameter	b	m	K ($\times 10^3$)	L ($\times 10^2$)	b	m	K ($\times 10^2$)	L ($\times 10^3$)
FVC, ℓ	-2.969±0.165	0.0365±0.0013	0.708	0.374	-2.442±0.152	0.0331±0.0013	0.663	0.374
FEV_1, ℓ	-2.469±0.148	0.0313±0.0012	0.639	0.336	-1.676±0.136	0.0256±0.0011	0.581	0.336
PEF, ℓ/sec	-3.846±0.569	0.0611±0.0046	2.393	1.288	-1.378±0.523	0.0402±0.0043	2.227	1.288
$FEF_{25-75\%}$, ℓ/sec	-1.644±0.414	0.0316±0.0033	1.739	0.936	-0.077±0.380	0.0174±0.0032	1.618	0.937
$\dot{V}max_{50\%}$, ℓ/sec	-2.111±0.482	0.0380±0.0039	2.026	1.090	-0.287±0.443	0.0209±0.0037	1.885	1.091
$\dot{V}max_{75\%}$, ℓ/sec	-0.256±0.347	0.0130±0.0028	1.485	0.786	0.466±0.319	0.0067±0.0026	1.390	0.786

SYMBOLS LEGEND FOR
WEIGHTED REGRESSION COEFFICIENTS TABLE
(Table 2)

* Regression equations have the form $y=mx + b$, where y represents the parameters; m, the slope with units equal to those of the parameter divided by cm; b, the intercept with units identical to the parameter; and x, the height in cm.

† Ninety-five percent confidence limits (for the regression line) for any height between 100 and 150 cm can be computed using the form $(mx + b) \pm Kx$, where K represents the 95% confidence coefficient.

** Ninety-five percent prediction limits (for an individual observation) for any height between 100 and 150 cm can be computed using the form $(mx + b) \pm Lx$, where L represents the 95% prediction coefficient.

†† Parameters are FVC (forced vital capacity), FEV_1 (forced expiratory volume in one second), PEF (peak expiratory flow), $FEF_{25-75\%}$ (forced expiratory flow during the middle half of the FVC), $\dot{V}max_{50\%}$ (maximum expiratory flow after 50% of the FVC has been exhaled), and $\dot{V}max_{75\%}$ (maximum expiratory flow after 75% of the FVC has been exhaled).

*** b = intercept $\pm$ S.E.

††† m = slope $\pm$ S.E.

TABLE 3

P-VALUES FOR TESTS OF NO DIFFERENCES
BETWEEN THE INDICATED REGRESSION LINES

Comparisons*	FVC	FEV_1	PEF	$FEF_{25-75\%}$	$\dot{V}max_{50\%}$	$\dot{V}max_{75\%}$
BF vs BM†	0**	0	<0.001	<0.001	<0.002	<0.2
WF vs WM	0	0	<0.003	<0.001	0	<0.2
BF vs WF	0	0	<0.002	0	0	<0.001
BM vs WM	0	0	0	0	<0.001	<0.001

* Comparisons are for the regression lines described in Table 2 between the important race/sex groupings.

† BF (Black females), BM (Black males), WF (White females) and WM (White males).

** 0 indicates p-value less than 10^{-5}.

TABLE 4

P-VALUES FOR TESTS OF NO DIFFERENCES
BETWEEN THE INDICATED REGRESSION LINE SLOPES

Comparisons*	FVC	FEV_1	PEF	$FEF_{25-75\%}$	$\dot{V}max_{50\%}$	$\dot{V}max_{75\%}$
BF vs. BM†	0**	0	<0.001	<0.002	<0.02	<0.1
WF vs. WM	<0.07	<0.001	<0.001	<0.002	<0.002	<0.2
BF vs. WF	0	0	<0.2	<0.002	<0.01	<0.1
BM vs. WM	<0.7	<0.07	0	<0.01	<0.01	<0.2

* Comparisons are for the slopes of the regression lines described in Table 2 between the important race/sex groupings.

† BF (Black Females), BM (Black Males), WF (White Females), and WM (White Males).

** 0 indicates p-value less than 10^{-5}.

TABLE 5

UNWEIGHTED REGRESSION COEFFICIENTS*
FOR SPIROMETRIC PARAMETERS
N=815

	BLACK FEMALES						BLACK MALES					
Parameters†	b	m	r^2	SD**	Mean	C.V.††	b	m	r^2	SD	Mean	C.V.
FVC, ℓ	-2.021	0.0272	0.831	0.188	1.093	17.2	-2.691	0.0332	0.883	0.185	1.122	16.4
FEV_1, ℓ	-1.542	0.0223	0.775	0.185	1.017	18.2	-2.271	0.0288	0.886	0.158	1.037	15.2
PEF, ℓ/sec	-3.355	0.0552	0.514	0.826	2.975	27.8	-5.291	0.0719	0.777	0.589	2.968	19.9
$FEF_{25-75\%}$, ℓ/sec	-0.433	0.0189	0.237	0.523	1.739	30.1	-1.926	0.0314	0.489	0.492	1.688	29.1
$\dot{V}max_{50\%}$, ℓ/sec	-0.746	0.0239	0.244	0.647	1.991	32.5	-2.242	0.0361	0.499	0.554	1.909	29.0
$\dot{V}max_{75\%}$, ℓ/sec	0.314	0.0067	0.066	0.388	1.080	35.9	-0.431	0.0130	0.177	0.430	1.068	40.3

	WHITE FEMALES						WHITE MALES					
Parameters	b	m	r^2	SD	Mean	C.V.	b	m	r^2	SD	Mean	C.V.
FVC, ℓ	-3.040	0.0370	0.756	0.242	1.596	15.2	-2.496	0.0335	0.805	0.230	1.616	14.2
FEV_1, ℓ	-2.528	0.0318	0.787	0.190	1.453	13.1	-1.672	0.0255	0.725	0.219	1.459	15.0
PEF, ℓ/sec	-3.868	0.0612	0.557	0.630	3.798	16.6	-1.335	0.0398	0.390	0.693	3.547	19.5
$FEF_{25-75\%}$, ℓ/sec	-1.854	0.0333	0.380	0.490	2.313	21.2	-0.043	0.0171	0.237	0.427	2.051	20.8
$\dot{V}max_{50\%}$, ℓ/sec	-2.281	0.0393	0.412	0.541	2.639	20.5	-0.255	0.0206	0.252	0.494	2.276	21.7
$\dot{V}max_{75\%}$, ℓ/sec	-0.519	0.0151	0.150	0.415	1.376	30.2	0.459	0.0068	0.064	0.363	1.293	28.1

SYMBOLS LEGEND FOR
UNWEIGHTED REGRESSION COEFFICIENTS
FOR SPIROMETRIC PARAMETERS
(Table 5)

* Regression equations have the form $y=mx + b$, where y represents the parameters; m, the slope with units equal to those of the parameter divided by cm; b, the intercept with units identical to the parameter; and x, the height in cm.

† Parameters are FVC (forced vital capacity), FEV_1 (forced expiratory volume in one second), PEF (peak expiratory flow), $FEF_{25-75\%}$ (forced expiratory flow during the middle half of the FVC), $\dot{V}max_{50\%}$ (maximum expiratory flow after 50% of the FVC has been exhaled), and $\dot{V}max_{75\%}$ (maximum expiratory flow after 75% of the FVC has been exhaled).

** Standard Deviation

†† Coefficient of Variation (C.V.) = SD ÷ Mean x 100.

TABLE 6

PEAK EXPIRATORY FLOW AS A FUNCTION OF HEIGHT IN BLACK FEMALES:
ORTHOGONAL POLYNOMIAL REGRESSION COEFFICIENTS* AND RELATED STATISTICS

Term	Coefficient	SD	t	p
Constant	11.677	0.822	62.850	0
Linear	14.701	0.821	17.902	0
Quadratic	2.029	0.821	2.472	0.014
Cubic	0.450	0.822	0.547	0.585
Quartic	0.429	0.821	0.422	0.602

* Note: Orthogonal polynomial regression has the property that the value of a specific coefficient (e.g., the linear term) does not depend upon the other terms included in the model. In a nonorthogonal regression, the value of the linear term, for example, would depend upon which other terms were included in the model.

TABLE 7

AVERAGE ESTIMATED VARIANCE (A.E.V.) STATISTICS FOR FOUR ORTHOGONAL POLYNOMIAL REGRESSIONS OF PEAK EXPIRATORY FLOW AS A FUNCTION OF HEIGHT IN BLACK FEMALES

Terms in model	A.E.V.
Linear	0.004532
Linear, quadratic	0.006683
Linear, quadratic, cubic	0.008932
Linear, quadratic, cubic, quartic	0.011193

TABLE 8

VARIABILITY OF 95% PREDICTION LIMITS
FOR FORCED VITAL CAPACITY

Race/Sex	100 cm Height			125 cm Height			150 cm Height		
	FVC*	Lim.†	%**	FVC	Lim.	%	FVC	Lim.	%
Black Females	0.704	0.371	52.7	1.370	0.464	33.9	2.039	0.557	27.3
Black Males	0.639	0.374	58.5	1.449	0.468	32.3	2.259	0.561	24.8
White Females	0.681	0.374	54.9	1.594	0.475	29.3	2.506	0.561	22.4
White Males	0.868	0.374	43.1	1.696	0.475	28.0	2.523	0.561	22.4

* FVC (forced vital capacity) computed from regression coefficients in Table 2.

† Lim. (Prediction Limit) computed from prediction limit coefficient given in Table 2 for Race/Sex specific FVC parameter x height.

** % computed as Lim. ÷ FVC x 100.

TABLE 9

COMPARISON OF SPECIFIC FLOW VALUES IN THE PRESENT STUDY WITH THOSE VALUES OBTAINED BY OTHERS

PEF

	130 cm				150 cm			
	WF	WM	BF	BM	WF	WM	BF	BM
Present study	4.097	3.848	3.791	3.992	5.319	4.652	4.853	5.362
Schoenberg (29)	3.18	3.18	3.03	3.10	4.33	4.36	4.35	4.27
Zapletal (27)	3.19	3.49	---	---	4.51	5.10	---	---
Hsu (26)	4.401	4.414	4.250	4.316	6.177	6.579	6.236	6.555

$FEF_{25-75\%}$

	130 cm				150 cm			
	WF	WM	BF	BM	WF	WM	BF	BM
Present study	2.464	2.185	2.042	2.120	3.096	2.533	2.432	2.700
Hsu	2.326	2.109	2.137	1.886	3.168	2.999	2.987	2.736

$\dot{V}max_{50\%}$

	130 cm				150 cm			
	WF	WM	BF	BM	WF	WM	BF	BM
Present study	2.829	2.430	2.365	2.402	3.589	2.848	2.855	3.062
Schoenberg	2.46	2.31	2.38	2.35	3.29	3.14	3.36	3.11
Zapletal	2.48	2.48	---	---	3.35	3.35	---	---

$\dot{V}max_{75\%}$

	130 cm				150 cm			
	WF	WM	BF	BM	WF	WM	BF	BM
Present study	1.425	1.337	1.192	1.250	1.685	1.471	1.338	1.488
Schoenberg	1.33	1.21	1.31	1.30	1.81	1.63	1.79	1.56
Zapletal	1.35	1.36	---	---	1.87	1.92	---	---

*See text for abreviations.

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SUMMARIES OF PUBLICATIONS

The following are summaries of publications that were supported in part by Environmental Protection Agency Grant #R804577:

Longitudinal observations have been made of a well-defined population of children in day care at the Frank Porter Graham Child Development Center in an investigation of the pathogenesis of infections due to respiratory syncytial virus (RSV) and Mycoplasma pneumoniae. A single RSV infection induced a modest but significant degree of resistance to further RSV infection in these children. Age and immunity seemed to interact to decrease the intensity of the clinical expression of illness associated with RSV infection. Infants and young children had asymptomatic or mild infections with M. pneumoniae; some of these children also became reinfected. A rise in titer of antibody to M. pneumoniae was demonstrated frequently in children of all ages. However, stimulation of peripheral lymphocytes by M. pneumoniae antigen was demonstrated infrequently in children younger than four years of age but frequently in children older than four years of age. It is speculated that the clinical expression of disease due to M. pneumoniae is modulated by immune responses; this hypothesis would explain the greater severity of illness in older children and young adults than in younger children. It is also speculated that RSV vaccines will not prevent RSV infection but may be expected to lessen the severity of clinical disease that follows such infections. M. pneumoniae vaccines probably should not be used in children because these vaccines may enhance immunity and increase the severity of illness. (1)

In an attempt to better understand acquired immunity to respiratory syncytial virus infections, we have analyzed data from a ten-year study of respiratory illness in normal children who were followed longitudinally from early infancy. Immunity was measured in terms of failure to become infected or reduction in severity of clinical illness upon reinfection. Outbreaks of infections occurred seven times over the ten-year period. During epidemics, the attack rate for first infection was 98 percent. The rate for second infections (75 percent) was modestly reduced (P less than 0.001); that for third infections was 65 percent. Age and history of infection both influenced illness. Immunity induced by a single infection had no demonstrable effect on illness associated with reinfection one year later; however, a considerable reduction in severity occurred with the third infection. These observations suggest that amelioration of illness---rather than prevention of infection---may be a realistic goal for immunoprophylaxis. (2)

The incidence, clinical manifestations, and infections etiology of respiratory illnesses observed in a prospective longitudinal study have been correlated with serum IgE values, which were used as objective markers of atopy. The incidence of wheezing illnesses was greater in children with elevated IgE levels, confirming an association previously reported. In contrast, the incidence of upper respiratory illness or middle ear disease showed no correlation with IgE values. The number and types of viral infections distributed evenly throughout the population. The results suggest that children with recurrent URI or MED deserve evaluation for allergy only if there are other clinical findings suggestive of atopy (3).

A prospective tympanometric and microbiologic study of 28 preschool children was undertaken to better define the effect of acute upper respiratory infections on induction of eustachian tube dysfunction. Significant negative middle ear pressure was present in 12.7 percent of tympanograms from well children. However, abnormal tympanograms were detected during 74.7 percent of acute upper respiratory tract infections. The abnormality was present on day one or two of illness in the majority of cases; 10.1 percent of illnesses were complicated by otitis media with effusion. Respiratory viruses or Streptococcus pyogenes were etiologically implicated in 40.5 percent of illnesses; isolation rates of Streptococcus pneumoniae and Haemophilus influenzae from well and ill children were similar. Although colonization of the nasopharynx of well children with Streptococccus pneumoniae or Haemophilus influenzae was associated with a higher incidence of abnormal middle ear pressure, colonization with Streptococcus pneumoniae or Haemophilus influenzae during upper respiratory tract infection did not influence the frequency of tympanogram abnormality (4).

Nasopharyngeal isolates of H. influenzae have been typed by the slide agglutination test, the Quellung reaction, the latex agglutination test, countercurrent immunoelectrophoresis, and the antiserum agar test. These tests gave essentially comparable results, with countercurrent immunoelectrophoresis and latex agglutination being slightly more sensitive. Cross-reactive problems encountered with latex agglutination and the expense of performing countercurrent immunoelectrophoresis or the antiserum agar test made these tests less practical than the slide agglutination test to identify single strains that were already isolated. The Quellung reaction and slide agglutination were the most rapid tests used to type an organism. For mass screening of multiple samples, countercurrent immunoelectrophoresis was the simplest technique. The antiserum agar test was slow but was the best technique to screen nasopharyngeal swab cultures to identify the presence of any encapsulated strains in the mixed flora. Whether any of the above techniques were as sensitive as the immunofluorescence test was not evaluated in this study (5).

A system for measuring parameters of ventilation and respiratory mechanics in intact anesthetized hamsters was developed. Means $\pm$ 1 standard deviation of five weekly measurements of these parameters in eight hamsters were 0.68 $\pm$ 0.09 ml for tidal volume, 45 $\pm$ 14 breaths $\cdot$ min^{-1} for respiratory frequency, 29.3 $\pm$ 10.4 ml/min^{-1} for minute ventilation, 0.301 $\pm$ 0.080 ml/cm H_2O^{-1} for dynamic compliance, 0.435 $\pm$ 0.151 $cmH_2O/ml^{-1}\cdot s$ for inspiratory resistance, 0.311 $\pm$ 0.101 $cmH_2O\cdot ml^{-1}.s$ for expiratory resistance, and 0.334 $\pm$ 0.096 $cmH_2O.ml^{-1}.s$ for average resistance. The standard deviations of five consecutive measurements of these parameters on the same day were typically 10% of the corresponding mean values, suggesting that acute changes as small as 10% can be detected in a study of similar size. The corresponding value for five single measurements on different days at weekly intervals was 30%. We believe that this system yields reasonable and repeatable measurements, and, because it is atraumatic, it can be used in chronic studies of diseases in hamsters and other small animals (6).

Total respiratory resistance (Rrs) and the fraction of this resistance located peripherally, (Fp) were measured in a group of children (3-5 years old). The technique used forced random noise to characterize the frequency dependence of effective resistance and an algorithm to compute Rrs and Fp from these data. The overall mean value $\pm$ SD for Fp was 0.534 $\pm$ 0.070; the mean value of 0.464 for the six children near 5 years of age was significantly different (P less than 0.001) from the mean value of 0.576 found in the younger children. The overall mean value $\pm$ SD for Rrs was 16.9 $\pm$ 5.8 $cmH_20.1^{-1}.s$; individual values appeared to be correlated with height. These results agree with previous reports indicating that children have a larger fraction of respiratory resistance in the periphery than do adults (7).

The frequency dependence of total respiratory impedance during spontaneous breathing was measured repeatedly in 16 children (3-5 years old) over a three-month period using forced random noise and spectral analysis. Total respiratory resistance, compliance, and inertance, which were calculated from the impedance data using regression analysis with a second-order model, had overall mean values $\pm$ SD of 5.61 $\pm$ 0.49 $cmH_20.1^{-1}.s$, 4.03 $\pm$ 1.04 $ml.cmH_20^{-1}$, and 0.0120 $\pm$ 0.0024 $cmH_20.1^{-1}.s^2$, respectively. Linear regression analysis showed that resistance and compliance correlated with either height or forced vital capacity with r values in the range 0.77-0.89. Analysis of measurement variability suggested that resistance measurements had, on the average, a coefficient of variation of 15%; corresponding values for compliance and inertance measurements were 25% (8).

Repeated measurements of spirometric parameters were made in two cohorts of young black children in a day care center when free of respiratory illness. All children were studied over a three-month period. Cohort 2 consisted of 8 children with average age of 63 months and average height of 109 cm. Cohort 3 consisted of 10 children who had an average age of 46 months and height of 102 cm. The means and standard deviations (SD) of each parameter for each child were computed. Average means $\pm$ average SD for spirometric parameters in Cohort 2 were 0.94 $\pm$ 0.065 ℓ for FVC, 0.91 $\pm$ 0.062 ℓ for FEV_1, 2.70 $\pm$ 0.354 ℓ/s for PEF, 1.66 $\pm$ 0.263 ℓ/s for $FEF_{25-75\%}$, 1.80 $\pm$ 0.312 ℓ/s for $\dot{V}max_{50\%}$, and 1.08 $\pm$ 0.219 ℓ/s for $\dot{V}max_{75\%}$. Means $\pm$ SD for Cohort 3 were 0.78 $\pm$ 0.065 ℓ for FVC, 0.77 $\pm$ 0.063 ℓ for FEV_1, 2.20 $\pm$ 0.248 ℓ/s for PEF, 1.54 $\pm$ 0.218 ℓ/s for $FEF_{25-75\%}$, 1.73 $\pm$ 0.241 ℓ/s for $\dot{V}max_{50\%}$ and 1.05 $\pm$ 0.201 ℓ/s for $\dot{V}max_{75\%}$. To compare the variability of these parameters in Cohort 3 to Cohort 2, average coefficients of variation (SD ÷ mean x 100) were computed. The average coefficients of variation for Cohort 2 were 7.0 for FVC, 6.9 for FEV_1, 13.1 for PEF, 15.2 for $FEF_{25-75\%}$, 16.9 for $\dot{V}max_{50\%}$, and 19.9 for $\dot{V}max_{75\%}$ and in Cohort 3 were 8.2 for FVC, 8.0 for FEV_1, 11.3 for PEF, 14.7 for $FEF_{25-75\%}$, 15.1 for $\dot{V}max_{50\%}$ and 20.0 for $\dot{V}max_{75\%}$. The coefficients of variation for these spirometric parameters in the younger cohort (Cohort 3) were similar to those obtained for the older cohort (Cohort 2) and were similar to the variability expected in older populations. This suggests that spirometry can be performed reliably in young children who have undergone a period of training (9).

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